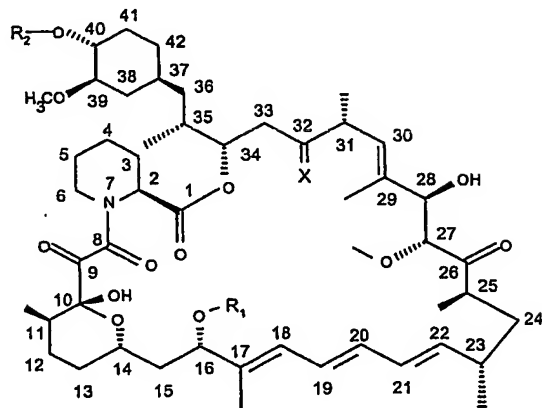


CLAIMS

1. Use of a rapamycin derivative of formula I



wherein

$R_1$  is  $\text{CH}_3$  or  $\text{C}_{3-6}$ alkynyl,

$R_2$  is H or  $-\text{CH}_2-\text{CH}_2-\text{OH}$ , 3-hydroxy-2-(hydroxymethyl)-2-methyl-propanoyl or tetrazolyl,

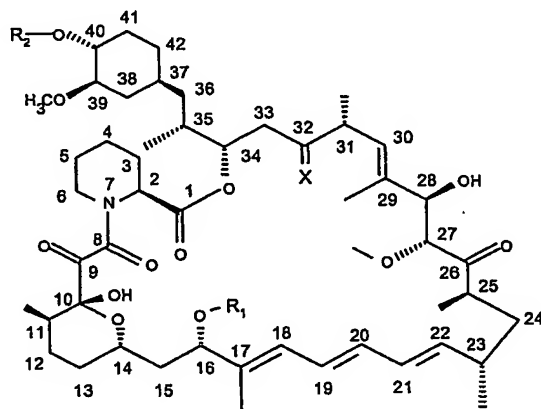
and X is  $=\text{O}$ , (H,H) or (H,OH),

provided that  $R_2$  is other than H when X is  $=\text{O}$  and  $R_1$  is  $\text{CH}_3$ ,

or a prodrug thereof when  $R_2$  is  $-\text{CH}_2-\text{CH}_2-\text{OH}$ , e.g. a physiologically hydrolysable ether thereof

in the preparation of a pharmaceutical composition for the treatment of abnormally increased bone turnover or resorption.

2. A pharmaceutical composition for use in the treatment of abnormally increased bone turnover or resorption comprising a rapamycin derivative of formula I



wherein

$R_1$  is  $\text{CH}_3$  or  $\text{C}_{3-6}$ alkynyl,

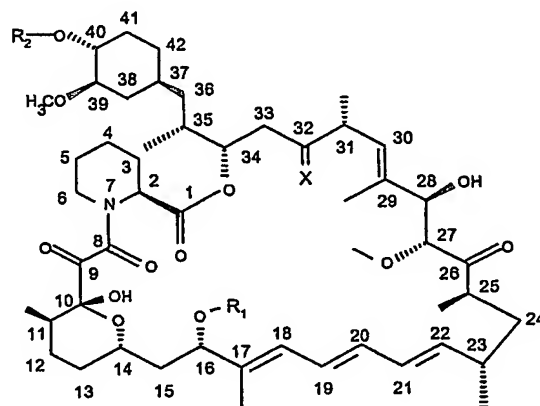
$R_2$  is H or  $-\text{CH}_2-\text{CH}_2-\text{OH}$ , 3-hydroxy-2-(hydroxymethyl)-2-methyl-propanoyl or tetrazolyl, and X is  $=\text{O}$ , (H,H) or (H,OH),

provided that  $R_2$  is other than H when X is  $=\text{O}$  and  $R_1$  is  $\text{CH}_3$ ,

or a prodrug thereof when  $R_2$  is  $-\text{CH}_2-\text{CH}_2-\text{OH}$ , e.g. a physiologically hydrolysable ether thereof,

together with one or more pharmaceutically acceptable diluents or carriers therefor.

3. A pharmaceutical combination comprising rapamycin or a rapamycin derivative and a second drug selected from bone resorption inhibitor, a calcitonin or an analogue or derivative thereof; a steroid hormone, a partial estrogen agonist or estrogen-gestagen combination; a selective estrogen receptor modulator; vitamin D or an analogue thereof; Parathyroid Hormone (PTH), a PTH fragment or a PTH derivative; a bisphosphonate; a cathepsin K inhibitor; a PTH releaser; a selective androgen receptor molecule; and strontium ranelate.
4. A method for treating abnormally increased bone turnover or resorption in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of a rapamycin derivative of formula I



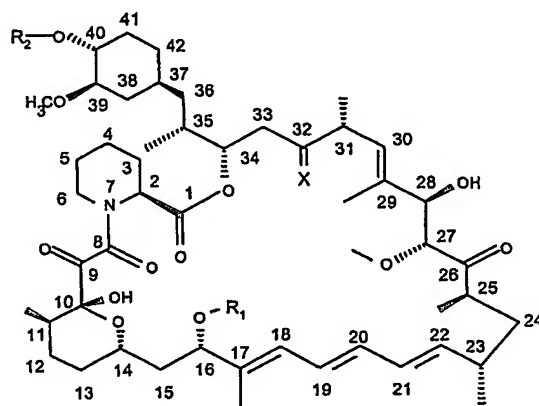
wherein

$R_1$  is  $\text{CH}_3$  or  $\text{C}_{3-6}$ alkynyl,

$R_2$  is H or  $-\text{CH}_2-\text{CH}_2-\text{OH}$ , 3-hydroxy-2-(hydroxymethyl)-2-methyl-propanoyl or tetrazolyl, and X is  $=\text{O}$ , (H,H) or (H,OH),

provided that  $R_2$  is other than H when X is  $=\text{O}$  and  $R_1$  is  $\text{CH}_3$ ,

- or a prodrug thereof when  $R_2$  is  $-\text{CH}_2\text{CH}_2\text{OH}$ , e.g. a physiologically hydrolysable ether thereof.
5. A method for treating abnormally increased bone turnover or resorption in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of rapamycin or a rapamycin derivative, concomitantly or sequentially with a second drug selected from bone resorption inhibitor, a calcitonin or an analogue or derivative thereof; a steroid hormone, a partial estrogen agonist or estrogen-gestagen combination; a selective estrogen receptor modulator; vitamin D or an analogue thereof; Parathyroid Hormone (PTH), a PTH fragment or a PTH derivative; a bisphosphonate; a cathepsin K inhibitor; a PTH releaser; a selective androgen receptor molecule; and strontium ranelate.
  6. Combination of claim 3 or method according to claim 5 wherein the rapamycin derivative is a compound of formula I



wherein

$R_1$  is  $\text{CH}_3$  or  $\text{C}_{3-6}$ alkynyl,

$R_2$  is H or  $-\text{CH}_2\text{CH}_2\text{OH}$ , 3-hydroxy-2-(hydroxymethyl)-2-methyl-propanoyl or tetrazolyl, and X is  $=\text{O}$ , (H,H) or (H,OH),

provided that  $R_2$  is other than H when X is  $=\text{O}$  and  $R_1$  is  $\text{CH}_3$ ,

or a prodrug thereof when  $R_2$  is  $-\text{CH}_2\text{CH}_2\text{OH}$ , e.g. a physiologically hydrolysable ether thereof.

7. Use, composition, combination or method according to any preceding claim wherein the rapamycin derivative is selected from 40-O-(2-hydroxyethyl)-rapamycin, 40-[3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate]-rapamycin, 40-epi-(tetrazolyl)-rapamycin, 32-deoxorapamycin, 16-pent-2-ynyloxy-32(S)-dihydro rapamycin, and TAFA-93.

8. Use, composition, combination or method according to any preceding claim wherein the rapamycin derivative is 40-O-(2-hydroxyethyl)-rapamycin.
9. Use, composition, combination or method according to any preceding claim for the treatment of osteoporosis; bone loss secondary to or due to medication; bone loss associated with immobilisation and space flight; bone loss associated with rheumatoid arthritis, osteopenia, osteogenesis imperfecta, hyperthyroidism, anorexia nervosa, organ transplantation, joint prosthesis loosening; periarticular bone erosions in rheumatoid arthritis; osteoarthritis; hypercalcemia; bone cancer and bone metastases; and/or multiple myeloma.